Manganese and Compounds

7439-96-5

Mn

I. Physical and Chemical Properties

Description	Lustrous, gray-pink metal (Mn); green (MnO), black (MnO_2) or pink ($MnCl_2$) crystals; brownish-black powder (Mn_3O_4)
Molecular formula	See above
Molecular weight	54.9 g/mol
Air concentration conversion	Not applicable

II. Overview

There is evidence from human studies and animal experiments that manganese exposure can lead to neurodevelopmental and behavioral effects. Neurotoxicity and developmental toxicity are two of the key toxicological endpoints of concern to infants and children. Animal studies show that newborns are particularly susceptible possibly because manganese homeostasis is not established until around the time of weaning (Miller et al., 1975). No direct human studies were found that would tell us whether human newborns would be especially vulnerable, but children do appear to be more susceptible to manganese poisoning during total parenteral nutrition (Komaki *et al*, 1999). Manganese appears to have the potential to differentially impact infants and children, however there is a low potential for manganese exposure. Methylcyclopentadienyl manganese tricarbonyl (MMT), an organic manganese compound, has been used as a gasoline additive in some locations, but its use is prohibited in California (California Code of Regulations, Title 13, Section 2254).

III. Principal Sources of Exposure

Metallic manganese is used in the manufacture of steel, stainless steel, and other metal alloys (HSDB, 1999). The most recent average ambient air level of manganese in California is 21 ng/m^3 (CARB, 1999). The annual statewide emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 105,000 lbs in 1998 (CARB, 1999). Thus, there is some concern about near-source exposures.

Individuals may be exposed to manganese dust by inhalation, or to manganese salts dissolved in drinking water sources. Foods (particularly nuts and grains) are a source of essential manganese. Adequate Intake (AI) for children 1 to 3 years of age is 1.2 mg Mn/day. AI is 2.3 mg/day for men, and 1.8 mg/day for women (Institute of Medicine, 2001). At the statewide average concentration, ambient

exposure would account for about one five-thousandth of the daily exposure. There is evidence in rats that inhaled manganese can be absorbed directly through the olfactory bulbs (Brenneman *et al*., 2000). This could theoretically increase the effect of inhaled manganese on the brain, but more research will be needed to address this question.

IV. Potential for Differential Effects

A. Summary of Key Human Studies

Studies of the effects of manganese exposure in both adults and children demonstrate the potential for neurological effects. As noted in the Introduction, neurotoxicity is one of the key toxicological endpoints of concern for infants and children. Male workers (n=92, plus 101 matched controls) in an alkaline battery plant in Belgium exposed to manganese dioxide dust were the subjects of a cross-sectional epidemiological study (Roels *et al*., 1992). The subjects were evaluated for neurobehavioral function, lung function, hematological parameters and by urinalysis. Significant decrements in performance on tests for visual reaction time, eye-hand coordination, and hand tremor were found in exposed workers relative to controls. Lifetime integrated respirable dust levels (LIRD) ranged from 0.04 to 4.43 mg Mn $\times$ years /m^3, with a geometric mean of 0.793 mg Mn $\times$ yrs/m^3. Average exposure time was 5.3 years (0.2 to 17.7 years). Similar results had been reported in an earlier study by the same group of investigators (Roels *et al*., 1987). There are no directly comparable studies in children. Neurobehavioral effects are likely to affect children differentially because children's nervous systems are developing, as discussed in the introduction.

Kilburn (1987) studied the aboriginal natives of Groote Eylandt, Australia. This island off the coast of Australia has long been a source of manganese ore. It had been informally observed that drinking water on the island is often discolored by manganese. Also, there had been reports of high incidence of birth defects among children born on the island. Kilburn compared the natives of this island with a group of mainland natives. He found that stillbirths were higher among the islanders (42 percent versus 29.5 percent) but did not give a statistical analysis of significance. During the study period of 1975 to 1985 there were 293 children born to the islanders. He reported on a number of congenital abnormalities, but admitted that the numbers were not sufficient for a statistical analysis of significance. He also reported on neurological disorders manifest as "problems of weakness, gait, coordination and ocular movements." Again, there is no statistical analysis. The results of this study are inconclusive though perhaps suggestive of adverse effects from manganese exposure.

Children receiving total parenteral nutrition (TPN) are at increased risk for hypermanganesemia, cholestasis, and basal ganglia damage (Fell *et al*., 1996). TPN appears to bypass the normal homeostatic controls on blood manganese levels. The normal "reference range" for manganese in the blood is 72 to 210 nmol/L. Eleven child patients on TPN who were identified as having hypermanganesemia and cholestasis had blood manganese levels of 615 to 1840 nmol/L. It is difficult to establish the order of causality, but these investigators are of the opinion that manganese may contribute to cholestasis. Cholestatic disease generally improved concomitant with blood manganese decline after reduction or withdrawal of manganese supplementation. The patients had been receiving

the usual recommended manganese dose of 1.0 µmol/kg per day for those less than 10 kg body weight, and 0.8 µmol/kg per day for those over 10 kg body weight. The authors recommend decreasing this to not more than 0.018 µmol/kg per day together with regular examinations of the nervous system (yearly cranial magnetic resonance imaging).

There are more recent reports of manganese causing problems for pediatric TPN patients (Kelly, 1998; Komaki *et al*., 1999). Kelly found that liver disease develops in 40 to 60% of infants who require long-term TPN for intestinal failure. Kelly points out that although there is clearly a relationship between manganesemia and liver disease, it is not clear which one causes the other. Cholestasis may contribute to hypermanganesemia because bile is the main route of excretion of manganese. Komaki *et al*. (1999) reported on a two-year-old female patient on TPN who experienced tremor and seizures resulting from accumulation of manganese in her brain. This patient had received 1.1 mg Mn per day (82 µg/kg per day). This would be equivalent to 1.5 µmol/kg per day, which is higher than the "recommended dose" discussed in the paper by Fell et al. (1996).

Collip *et al*. (1983) reported elevated hair manganese in children with learning disabilities (hyperactivity). Hair manganese levels in eight-year-old children were 0.268 µg/g in normal children and 0.434 µg/g in learning disabled children. Similarly, Barlow (1983) reported a mean level of 0.84 µg Mn/g hair in 68 hyperactive children compared to a mean of 0.68 µg/g in control children. It is not known whether this is due to higher exposure to manganese or to a lower elimination rate of manganese in children. More work will be needed to determine if manganese exposure causes learning disabilities in exposed children, and, if so, at what exposure levels this effect would occur. No discussion of lead as a confounder was presented in this paper.

Collip *et al*. (1983) also found that formula-fed infants had significantly greater increases in hair manganese than breast-fed infants. The amount of manganese in infant formulas may be greater than optimal. Collip *et al*. (1983) reported that whereas human milk had only 10 µg Mn per quart, commercial infant formulas generally ranged from 200 to 1,000 µg Mn per quart.

B. Summary of Key Animal Studies

Animal experiments demonstrate that exposure to excess manganese can lead to accumulation of manganese in critical areas of the brain. This in turn can lead to changes in brain chemistry and neurological dysfunction. Neonatal animals appear to be particularly vulnerable to accumulation of manganese in critical brain areas because manganese homeostasis is not established until later.

Newborn mice are unable to excrete injected manganese for the first 17 days of life (Miller *et al*, 1975). During this period manganese accumulates in the tissues, particularly in the liver and brain. After this period manganese is excreted and homeostasis of manganese is maintained. This inability to control manganese levels in tissues by excretion might make neonatal animals more susceptible to manganese poisoning.

Experiments in farm animals and laboratory animals (rats) indicate that manganese homeostasis is "suspended" during pregnancy and lactation (reviewed by Cawte, 1985). Suspension of homeostasis allows for higher levels of manganese in blood and in tissues including brain.

In discussing studies with mice (their own and others), Webster and Valois (1987) state, "The neonate is clearly the stage of human development potentially at the greatest risk from environmental manganese. The high intestinal absorption, absent excretory mechanism and ready accumulation in the developing brain all combine to make this a period of concern." The neonate appears to be more vulnerable than the fetus (Webster and Valois, 1987) because of the inability of the neonate to maintain manganese homeostasis. Kontur and Fechter (1985) also state that, "Neonatal animals show differential absorption, accumulation, and excretion of manganese relative to adults."

Dorman *et al*. (2000) studied the relative sensitivity of neonatal and adult CD rats to manganese-induced neurotoxicity. The rats were administered $MnCl_2$ orally at doses of 0, 25, or 50 mg/kg. These doses were given to neonatal rats during lactation, and to adult rats for 21 consecutive days. All rats were evaluated in behavioral and neurochemical tests. Increased pulse-elicited acoustic startle response amplitude was observed in neonates from both manganese chloride treatment groups on post natal day (PND) 21. Increased striatal, hippocampal, hindbrain and cortical manganese concentrations were observed in all manganese-exposed neonates on PND 21. Increased striatal, cerebellar and brain residue manganese concentrations were observed in adult rats from the high dose group. The authors conclude, "neonates may be at greater risk for manganese-induced neurotoxicity when compared to adults receiving similar high oral levels of manganese."

Young rats (starting at 21 days of age) showed neuronal degeneration (characterized by fewer nuclei per unit area with less staining per nucleus) in cerebral and cerebellar cortex after 30 days of administration of 50 µg $MnCl_2$ per day (Chandra and Shukla, 1978). Similar neuronal degeneration appeared in adult rats only after 120 days of Mn administration at the same exposure level.

Pappas et al. (1997) exposed female rats and their litters to manganese in drinking water from conception until PND 30. The concentrations of manganese in the water were 0, 2, and 10 mg/ml. Body weight gain was decreased significantly in the high dose group, but not in the low dose group. Cortical levels of manganese were 35% higher than controls in the low dose group (not statistically significant) and 150% higher in the high dose group. Behavioral testing of the pups showed significantly increased locomotor activity and rearing in the high dose, but not the low dose group. Other behavioral tests (radial arm maze, Morris water maze) showed no significant differences between exposed and control rats. There was a significant decrease in cortical thickness in pups of both exposed groups relative to the controls. The investigators were not able to determine the exact cause of the cortical thinning (decreased cell number, reduction in cell size, reduced arborization, etc.). They speculated that it may have been due to malnutrition, as it was seen only in rats with significantly reduced body weight gain. Brain cytochemistry tests on the rats included choline acetyltransferase, glial fibrillary acidic protein, tyrosine hydroxylase and mesencephalic dopamine. None of these cytochemical tests showed any significant differences between exposed and control rats.

Lown *et al*. (1984) found significantly increased activity in pups of mice exposed to MnO_2 dust by inhalation during and after pregnancy. Brenneman *et al*. (1999) observed hyperactivity in PND 21 pups of CD rats exposed to $MnCl_2$ in drinking water at a dose of 50 mg/kg bw.

Deskin, Bursian and Edens (1980) exposed male rats from birth to 24 days to 1, 10 and 20 µg/g bw $MgCl_2$ by oral gavage. Body weight gain was unaffected at all doses. Dopamine (but not norepinephrine) was reduced in the hypothalamic areas of rats exposed to 10 and 20 µg/g $MnCl_2$. The depletion of dopamine induced by alpha-methyl-p-tyrosine (a tyrosine hydroxylase inhibitor) was less in the hypothalamic areas of chronic manganese-treated rats, suggesting that dopamine turnover was reduced.

Not all the studies of neurotoxicity from early-in-life exposures have been positive. Kontur and Fechter (1985) exposed pregnant rats to 0, 5, 10, or 20 mg/ml of manganese chloride ($MnCl_2$) in drinking water. They found that the higher doses (10 and 20 mg/ml) were sufficient to cause a significant decrease in maternal weight gain. The highest dose caused a significant decrease in average litter size. The investigators showed that manganese crossed the placenta and accumulated in the fore- and hindbrains of the pups. However, the accumulation of manganese in the brains of the rat pups was limited; increasing the exposure beyond 5 mg/ml did not result in increased accumulation of manganese in the brains. The investigators looked at catecholamine turnover and development of acoustic startle response in newborn pups that had been exposed to manganese *in utero*. They found that neither of these parameters was significantly affected by manganese exposure. The authors conclude that although manganese exposure in utero causes reduced maternal weight gain and reduced litter size it is not specifically neurotoxic to newborn rats exposed *in utero* (Kontur and Fechter, 1985).

Webster and Valois (1987) injected pregnant mice i.p. with 12.5, 25 and 50 mg manganese sulfate/kg. An increase in fetal death and decrease in fetal weights were observed in all dose groups. Exencephaly was induced with 25 mg/kg on gestation day (GD) 8. The higher dose (50 mg/kg) induced fetal deaths, but no exencephaly. The authors state that the exencephaly observed at 25 mg/kg is "probably of little significance in view of the high dose necessary for teratogenesis." Colomina *et al*. (1996) investigated the relationship between day of exposure and embryo/fetotoxicity in mice injected s.c. with 50 mg manganese chloride/kg on days 9, 10, 11 and 12 of gestation. No teratogenic effects were observed in this study. Days 9 and 10 of gestation were determined to be the most sensitive for embryotoxicity evidenced by significant increases in late resorptions and increased incidence of postimplantation loss. Days 9 and 10 were also the most sensitive for fetotoxicity (reduced fetal body weight and increased incidence of skeletal defects).

Treinen *et al*. (1995) exposed pregnant Sprague-Dawley rats to manganese chloride via tail-vein injection on GD 6-17. Dosages included 5, 20 or 40 µmol/kg. At the two higher doses they observed specific skeletal variations: wavy ribs and reduced ossification.

In a study involving subcutaneous injection of pregnant Swiss albino mice, Sanchez *et al*. (1993) reported a NOAEL of 2 mg/kg/day $MnCl_2$ for embryotoxicity and skeletal variations.

V. Additional Information

A. Regulatory Background

The California chronic Reference Exposure Level (REL) for manganese is 0.2 $\mu g/m^3$. It is based on a human study (discussed above) showing neurobehavioral effects, by Roels *et al*. (1992). In this study, workers were classified according to their integrated lifetime exposure to manganese dioxide dust (ranging from < 0.6 to >1.2 mg Mn × yrs/m^3). The geometric mean for all exposed workers of the integrated lifetime occupational exposure, divided by the mean occupational exposure duration, was used as a LOAEL (0.15 mg Mn/m^3) to calculate the REL.

VI. Conclusions

There is evidence from both human studies and animal experiments that manganese may exert a differential toxic effect on infants and children. Human studies show that hyperactive children and children with learning disabilities may have higher hair levels of manganese than normal children (Collip, Chen and Maitinsky, 1983). This suggests that manganese may act as a neurodevelopmental toxicant on young children. Animal studies show that newborn animals are unable to maintain homeostasis of manganese (Miller et al., 1975) and that as a result manganese accumulates in the brains of animals exposed at young ages (Dorman et al., 2000). There is also evidence that manganese exposure to young animals can cause neurodegenerative changes such as neuronal degeneration and cortical thinning (Chandra and Shula, 1978; Pappas et al., 1997).

Manganese does not appear to be a major hazard from the point of view of widespread air exposures. Although ambient air levels may be higher near sources, the general statewide ambient levels are low (21 ng/m^3). Assuming a child breathes 10 m^3 of air daily, the amount of manganese to which the child would be exposed by air at this ambient level would be about one five-thousandth of the amount needed in the diet to fulfill the adequate intake level (1.2 mg Mn/day). OEHHA has placed manganese in Tier 2 primarily because of current low potential for airborne exposures. Should new information become available indicating significant exposures, manganese should be reconsidered for listing under SB25.

VII. References

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